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ORIGINAL ARTICLE

Respiratory syncytial virus prophylaxis in infants with congenital airway anomalies compared to standard indications and complex medical disorders

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Abstract

An observational study was conducted of children < 2 years who received ≥ 1 dose of palivizumab in 32 Canadian institutions from 2005 to 2017. We compared respiratory illness (RIH) and respiratory syncytial virus-related hospitalization (RSVH) hazards in children with a congenital airway anomaly (CAA) versus those prophylaxed for standard indications (SI) and serious medical disorders (SMD). Data were assembled on neonatal course, demographics, palivizumab utilization and adherence, and respiratory illness events, and analyzed using ANOVA, chi-square tests and Cox proportional hazards. Twenty-five thousand three children (1219 CAA, 3538 SMD, and 20,246 SI) were enrolled. Palivizumab adherence was 74.8% overall and similar across groups. For 2054 respiratory-related events, 1724 children were hospitalized. RIH rates were 13.6% (CAA), 9.6% (SMD), and 6.0% (SI). RSVH rates were 2.4% (CAA), 1.6% (SMD), and 1.5% (SI). After adjustment for demographic and neonatal differences, children with a CAA had a significantly increased RIH and RSVH hazard relative to SI (RIH, HR = 1.6, 95% CI 1.2–2.2, $p = 0.002$; RSVH, HR = 2.1, 95% CI 1.0–4.4, $p = 0.037$) but similar to SMD (RIH, HR = 1.3, 95% CI 0.9–1.9, $p = 0.190$; RSVH, HR = 1.7, 95% CI 0.7–4.1, $p = 0.277$).

Conclusion: Children with a CAA experience higher RIH risk. RSVH hazard was similar between CAA and SMD but higher for CAA compared to SI, implying that this population requires surveillance for RSV prophylaxis.

What is Known:
- *Children with congenital airway anomalies (CAA) are at risk for respiratory tract illness and respiratory syncytial virus-related hospitalization (RSVH) with accompanying morbidity and mortality*
- *RSV prophylaxis may be useful in children with a CAA, but is not routinely recommended*

What is New:
- *Children with a CAA had a 1.6–2.3 fold greater risk of respiratory-related hospitalization and RSVH compared to those prophylaxed for standard, approved indications and serious medical disorders.*
- *RSVH risk in children aged < 2 years with either upper or lower airway anomalies is similar. Children with a CAA require careful surveillance during the RSV season and prophylaxis may be appropriate.*

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Keywords Congenital airway anomalies · Respiratory syncytial virus · Palivizumab · Outcomes

Abbreviations

CAA	Congenital airway anomalies
RIH	Respiratory illness hospitalization
RSV	Respiratory syncytial virus
RSVH	Respiratory syncytial virus hospitalization
SI	Standard indications
SMD	Serious medical disorders

Introduction

Respiratory syncytial virus (RSV) is the dominant viral pathogen causing acute lower respiratory tract illness in children aged < 2 years [1–5]. In the majority of children, RSV infections are mild and symptoms are similar to a plethora of viruses that cause a brief upper respiratory tract, self-limited illness. However, premature infants, those with chronic lung disease and significant congenital heart disease are at greater risk of RSV-related hospitalization (RSVH) and incur substantial morbidity and mortality [6–8]. In 2015, it was estimated that approximately 59,600 in-hospital, RSV-related deaths occurred globally in children aged < 5 years [7]. In industrialized countries, the highest case-fatality rates involve children with pre-existing medical disorders such as chronic lung disease, neurologic, congenital heart and genetic disorders, airway abnormalities, and immunodeficiency [6].

Children with both upper and lower congenital airway anomalies (CAA) that extend from the nasal aperture to cystic malformations of the lung comprise a high-risk group for respiratory morbidity. Children aged < 2 years with a CAA are at increased risk for RSV infection, RSVH, intensive care unit admission, mechanical ventilation, prolonged intensive care, hospital length of stay, and death [9–13]. Kristensen et al. [11] in a Danish RSV database study conducted in the pre-palivizumab era from 1997 to 2003 reported that the adjusted incidence rate ratios for RSVH in 109 children with a CAA ranged from 1.38–2.20 with a mean incidence of 9.4%.

Palivizumab is a safe, humanized monoclonal antibody that is approved for prophylaxis against serious lower RSV-related respiratory tract infections in high-risk children [14, 15]. The American Academy of Pediatrics [16] and the Italian Neonatal Society [17] position statements on RSV prophylaxis recommend that children with a CAA may be considered for palivizumab in the first year of life while the Canadian Pediatric Society [18] states that these children should not be routinely offered prophylaxis during the RSV season. In Canada, the use of palivizumab for children with a CAA is adjudicated individually prior to the onset of the RSV season and is approved by an advisory board that works collaboratively with each provincial Ministry of Health.

The impact of RSV prophylaxis in CAA has not been systematically evaluated and published data in this field is extremely scarce. The primary objective of this study was to compare the hazard for respiratory-illness hospitalization (RIH) and RSVH in children with a CAA who received palivizumab during the RSV season, versus children prophylaxed for serious medical disorders (SMD), and for standard indications (SI). The secondary objective was to determine if there was a difference in RIH and RSVH in children with upper versus lower airway malformations.

Methods

The Canadian RSV Evaluation Study of Palivizumab is a prospective, observational, study that commenced in 2005 [19]. The registry monitors palivizumab usage and adherence to monthly palivizumab injections during the RSV season (November to March of the following year) and assesses respiratory illness-related events monthly. There are 32 participating sites located across Canada. Any child who receives at least one injection of palivizumab during the respective RSV season is eligible for enrollment. Children are excluded if they are receiving any other similar monoclonal antibody within a clinical trial, or if their parents or caregivers are unable to communicate in English or French. Children are enrolled at the start of the RSV season after the first dose of palivizumab and preferably before the third injection to facilitate sequential data collection on each subject. Research ethics board approval is obtained at each participating site and informed, written consent is procured for all subjects prior to enrollment. At enrollment, baseline information is collected regarding demographics, medical history, neonatal course, and palivizumab administration. Follow-up telephone interviews are conducted monthly to ascertain palivizumab utilization and adherence, alterations in baseline data, adverse events, and complications associated with a respiratory illness event.

In the event of a hospitalization, relevant details of the hospital course are excerpted from the patient's medical records after parental or legal guardian approval. Data are collected on diagnoses at the time of hospital admission, laboratory confirmation of RSV, requirement for respiratory support (invasive and non-invasive), oxygen therapy, intubation, mechanical ventilation, and duration of hospital stay. RSV diagnosis is established by polymerase chain reaction, enzyme or immunofluorescent assay, or viral culture on nasopharyngeal swabs, aspirates, or washes obtained from the patients during their hospital stay. A RIH with a positive RSV test confirmed by any of the detection methods is categorized as a RSVH.

Study definitions

A congenital malformation of the airway was defined as any anomaly involving the upper or lower respiratory tract, identified after birth. Upper airway anatomical anomalies included those involving the nasal passage (e.g., choanal atresia or severe stenosis), laryngomalacia, and primary vocal cord paralysis, extending to the subglottic region [20]. Lower airway abnormalities were classified as those extending from the subglottic area to pulmonary airway malformations (e.g., cystic adenomatoid malformation, pulmonary sequestration, lung cysts, lobar emphysema) [21]. Subjects presenting with a CAA anomaly were selected from the Canadian RSV Evaluation Study of Palivizumab regardless of any other coexisting medical conditions such as bronchopulmonary dysplasia, congenital heart disease, or cystic fibrosis. Only children aged < 2 years were included in order to conform to pediatric advisory guidelines. The assembled cohort was further sub-classified into upper and lower airway anomalies and those who received prophylaxis primarily for a CAA versus children who had a CAA but received prophylaxis as part of the SI and SMD groups. Children with a SMD comprised those with serious medical conditions such as cystic fibrosis, neuromuscular impairment, or immunodeficiency. Children in the SI category included those currently approved for palivizumab by the majority of international consensus guidelines (premature infants ≤ 35 completed weeks gestational age, children with bronchopulmonary dysplasia (chronic lung disease), and hemodynamically significant congenital heart disease [16–18, 22].

Palivizumab adherence was defined by the receipt of either ≥ 5 or at least the expected number of injections during the RSV season, and within the recommended time intervals between injections [23]. The definition is based on large pharmacokinetic and clinical studies utilizing palivizumab [24–26]. The accepted time intervals for palivizumab administration in the Canadian RSV Evaluation Study of Palivizumab were 16–35 days between the first and second injection and 25–35 days between subsequent injections. It is important to note that children with a CAA are not routinely offered RSV prophylaxis in Canada and provincial approval is granted individually on a case-by-case basis, after adjudication by members of an advisory board that work collaboratively with each provincial Ministry of Health.

Statistical analyses

Data were analyzed using IBM SPSS Statistics v25.0 (IBM Corp., Armonk, NY). Baseline demographics, neonatal characteristics, and clinical parameters were compared between the 3 groups (CAA, SMD and SI) using the Pearson chi-squared test for categorical variables and ANOVA for continuous variables. Median values and interquartile ranges are reported for continuous, non-normally distributed demographic variables. Kruskal-Wallis test was used to determine differences in medians of continuous variables with non-parametric distribution. Neonatal continuous and normally distributed variables were reported as mean values and standard deviations. A p value < 0.05 was considered statistically significant.

For descriptive purposes, unadjusted RIH and RSVH incidences were calculated. Cox proportional hazard regressions using a backwards conditional method were performed to evaluate the relative risk of RIH and RSVH between children with a CAA versus the SMD and SI groups respectively. Hazard for the respective events was gauged by the number of days from enrollment to the patient's first RIH or RSVH. Demographic and neonatal variables that were significantly different between the groups ($p < 0.05$) were adjusted as covariates in the analysis of time to first RIH or RSVH. Hazard ratio (HR), 95% confidence interval (95% CI), and p values are reported for each individual regression analysis. RSVH burden was evaluated using the Pearson chi-square test and ANOVA. Cox proportional hazard regressions were also used in post hoc analyses to compare risk of RIH and RSVH between upper and lower airway malformations and infants who received prophylaxis primarily for CAA only versus those who had a CAA but received prophylaxis principally as part of the SI and SMD groups.

Results

Over the 12 RSV seasons (2005–2017), 25,003 children who received palivizumab were enrolled; CAA ($n = 1219$, 4.9%), SMD ($n = 3538$, 14.2%), and SI ($n = 20{,}246$, 81.0%). On average, children received 4.4 ± 1.3 (SD) injections; 83.8% of their expected injections for the respective RSV season and 74.8% of their injections within appropriate time intervals. In total, 16,231 (64.9%) children were fully adherent based on both adherence definitions. Mean (SD) number of injections in the CAA, SMD, and SI groups were 4.7 ± 1.2, 4.6 ± 1.2, and 4.3 ± 1.4 respectively ($F = 92.2$, df = 2, $p < 0.0005$). Overall compliance was similar across groups (74.0% CAA, 76.3% SMD, and 74.6% SI ($\chi^2 = 5.1$, df = 2, $p = 0.077$)). Table 1 compares the baseline demographics between the 3 groups of children. All variables were significantly different between the study groups ($p < 0.05$). A higher proportion of children with a CAA was Caucasian and had a family history of atopy than the SMD and SI groups. Comparison of the neonatal course is depicted in Table 2. Children with a CAA had a higher gestational age and higher median birth weight compared to the SMD and SI groups.

Respiratory illness and RSV-related hospitalizations are described in Table 3. For 2054 respiratory-related events, 1724 children were hospitalized. Of the 1219 CAA subjects,

Table 1 Demographic characteristics of patients enrolled in the study ($n = 25,003$)

n (%)	CAA ($n = 1219$)	SMD ($n = 3538$)	SI ($n = 20,246$)	χ^2 or H	*p* value
Male	669 (54.9)	1915 (54.3)	11,499 (56.8)	9.2	*0.010*
Caucasian	916 (75.1)	2552 (72.1)	13,695 (67.6)	53.3	*< 0.0005*
Aboriginal	42 (3.4)	99 (2.8)	846 (4.2)	16.0	*< 0.0005*
Daycare attendance	84 (6.9)	361 (10.2)	522 (2.6)	503.6	*< 0.0005*
Smoking exposure in home	297 (24.4)	842 (23.8)	5972 (29.5)	58.5	*< 0.0005*
Siblings	752 (61.7)	2341 (66.2)	12,886 (63.6)	11.0	*0.004*
Siblings in daycare or school-aged	440 (49.6)	1175 (49.8)	6054 (44.1)	34.1	*< 0.0005*
Multiple birth	122 (10.0)	638 (18.0)	6189 (30.6)	437.8	*< 0.0005*
≥5 people in the household	246 (20.2)	762 (21.5)	5037 (24.9)	29.5	*< 0.0005*
Atopy in the family	549 (45.3)	1470 (42.0)	8015 (39.8)	19.5	*< 0.0005*
Enrollment age, months‡	7.0 [3.2–13.8]	8.1 [3.3–14.9]	3.1 [1.5–5.7]	2124.0	*< 0.0005*
Gestational age, wk‡	38.0 [35.1–39.2]	37.6 [34.7–39.1]	31.9 [29.1–34.1]	4106.9	*< 0.0005*
Pre-term birth	111 (9.1)	196 (5.5)	16,312 (80.6)	9498.6	*< 0.0005*
Birth weight, g‡	2900.0 [2160.0–3352.0]	2803.0[2060.0–3295.0]	1630.0 [1165.0–2150.0]	3437.2	*< 0.0005*
Enrollment weight, g‡	6980.0 [4948.0–9051.0]	7290.0 [5000.0–9400.0]	3970.0 [2800.0–5940.0]	3297.1	*< 0.0005*

‡Results as median [IQR]; df = 2; $p < 0.05$ is statistically significant

166 were hospitalized for a total of 207 respiratory illness events. 19.4% (334/1724) hospitalized children were RSV-positive; 26 (CAA), 51 (SMD), and 257 (SI). The burden of illness as depicted by the variables in association with RSVH is shown in Table 4. A higher proportion of RSV-positive children with a CAA were hospitalized with pneumonia, compared to the SMD and SI groups.

Cox proportional hazard analysis was adjusted for potential confounders as shown in Tables 1 and 2, including number of palivizumab injections. Hazard plots are shown in Fig. 1a for RIH and Fig. 1b for RSVH. Children with a CAA had a higher RIH hazard compared to the SI group but were similar compared to SMD (Table 5). Children with a CAA were also at a higher risk for RSVH compared to those who received prophylaxis for SIs but were similar to the SMD group (Table 5).

A sub-analysis of the CAA group was conducted to determine whether there were differences in risk of RIH and RSVH between those with upper ($n = 666$) and lower ($n = 553$) airway anomalies while controlling for potential confounding variables indicated in Tables 6 and 7. Children with upper airway anomalies were similar to those with lower airway anomalies for both RIH and RSVH hazard (Table 6).

In a subgroup of children primarily prophylaxed for CAA ($n = 852$) independent of comorbidities, differences in risk of RIH and RSVH were also assessed post hoc. Children with a CAA only had a higher RIH hazard ratio compared to SI and SMD groups; however, RSVH hazards were similar across the groups (Table 7). All analyses were adjusted for pertinent variables as shown in Tables 1 and 2, including number of palivizumab injections administered.

Table 2 Clinical characteristics of the subjects during the neonatal hospital course

	CAA ($n = 1219$)	SMD ($n = 3538$)	SI ($n = 20,246$)	χ^2 or *F*	*p* value
Days of neonatal stay (mean ± SD)	59.4 ± 82.4	43.0 ± 79.4	49.2 ± 63.7	26.5	$p < 0.0005$
Respiratory support (%)	675 (55.4)	1310 (37.0)	12,997 (64.2)	936.9	$p < 0.0005$
Duration in days (mean ± SD)	37.4 ± 64.8	31.7 ± 68.9	22.6 ± 31.4	76.4	$p < 0.0005$
Oxygen therapy (%)	663 (54.4)	1402 (39.6)	10,170 (50.2)	150.9	$p < 0.0005$
Duration in days (mean ± SD)	47.0 ± 84.4	33.0 ± 65.7	33.8 ± 59.3	14.3	$p < 0.0005$
Documented necrotizing enterocolitis (%)	37 (3.0)	66 (1.9)	620 (3.1)	15.5	$p < 0.0005$
Surgery for patent ductus arteriosus (%)	70 (5.7)	98 (2.8)	989 (4.9)	34.1	$p < 0.0005$
Documented sepsis (%)	222 (18.2)	368 (10.4)	2714 (13.5)	52.0	$p < 0.0005$

df = 2; $p < 0.05$ is statistically significant

Table 3 Respiratory illness and RSV-related hospitalization in the recruited subjects

	CAA	SMD	SI	Total
Hospitalized for respiratory illness (RIH)	166 (13.6%)	341 (9.6%)	1217 (6.0%)	1724 (6.9%)
Tested for RSV	147 (12.1%)	297 (8.4%)	1030 (5.1%)	1474 (5.9%)
RSV-related hospitalization (RSVH)	26 (2.1%)	51 (1.4%)	257 (1.3%)	334 (1.3%)
RSVH Incidence	2.4%	1.6%	1.5%	1.6%

Discussion

In the present study, children with a CAA had a 1.6–2.3-fold higher risk of RIH and RSVH compared to SI but not those with SMD. Children with a CAA are usually diagnosed antenatally with confirmation soon after birth with relevant investigations. Early neonatal management hinges on the presence of respiratory compromise associated with the respective anatomical lesion. Some abnormalities such as severe choanal atresia, tracheo-esophageal fistula, large cystic adenomatoid malformations, or congenital lobar emphysema cause severe respiratory distress and require early surgical intervention. Expectant management is adopted for smaller lesions that do not cause respiratory embarrassment but is not standardized [27, 28]. Irrespective of whether a child does or does not undergo surgical correction, children with a CAA are at risk for respiratory illness and lower respiratory infection during infancy and early childhood [29, 30].

In 1999, Arnold et al. [9] were the first investigators to report morbidities incurred in twenty children with a CAA and nine specifically with a tracheo-esophageal fistula who developed RSV infection. Forty-one percent required intensive care admission and 27.6% were mechanically ventilated. The median hospital stay was 12 days (range 2–52 days). More recently, Kristensen et al. [11] confirmed that children with a CAA involving both the upper and lower airways were a vulnerable population at high risk for RSV infection and hospitalization. The investigators reported a RSVH incidence that ranged from 6.4–13.7%. In the KID's inpatient database in the USA, the incidence of RSVH in infants with a CAA increased by 4.3% ($p = 0.41$) between 1997 and 2012 [31]. The morbidity and mortality experienced by children with a CAA who acquire RSV infection is substantial. In a retrospective medical chart review conducted over 3 RSV seasons (1994–1997), prior to the use of RSV prophylaxis, Buckingham et al. [10] reported that 5 children with upper airway anomalies had a protracted disease course involving prolonged duration of ventilation, intensive care stay, and hospital stay compared to children with normal upper airways. In a UK study, Thorburn [13] documented that among 406 RSV-positive patients admitted to the intensive care unit between1997–2007, 9% of the 35 deaths were attributed to large-airway abnormalities. Moreover, RSV also poses a significant risk during reconstructive surgery of airway malformations resulting in major perioperative complications, while extending both hospital stay in intensive care and inpatient units [32, 33]. Otolaryngologists recommended either seasonal surgery or preoperative RSV prophylaxis for children with a CAA lesion to avoid morbidity.

Table 4 Burden of illness associated with respiratory syncytial virus hospitalization among the recruited subjects ($n = 414$ RSV hospitalizations)

n = number of RSV hospitalizations	CAA ($n = 34$)	SMD ($n = 72$)	SI ($n = 308$)	χ^2 or F	p value
Apnea, n (%)	1 (2.9)	6 (8.3)	52 (17.0)	7.5	*0.021*
Bronchiolitis, n (%)	19 (55.9)	43 (59.7)	231 (75.5)	11.2	*0.003*
Decreased oxygen saturation, n (%)	16 (48.5)	34 (50.0)	136 (46.1)	0.3	0.818
Inability to maintain oral intake, n (%)	16 (47.1)	27 (37.5)	126 (41.2)	0.9	0.642
Pneumonia, n (%)	14 (41.2)	20 (27.8)	55 (18.0)	11.7	*0.003*
Respiratory arrest, n (%)	0 (0.0)	4 (5.6)	8 (2.6)	2.9	0.214
Respiratory distress, n (%)	27 (79.4)	56 (77.8)	220 (72.4)	1.5	0.493
Respiratory support required, n (%)	12 (35.3)	24 (33.3)	104 (33.8)	0.0	> 0.999
Days on respiratory support (mean ± SD)	3.8 ± 8.6	1.7 ± 3.3	2.7 ± 6.7	1.3	0.285
Length of hospital stay in days (mean ± SD)	7.1 ± 7.8	8.1 ± 9.7	7.9 ± 11.0	0.1	0.886
ICU admission, n (%)	9 (26.5)	15 (20.8)	88 (28.6)	1.8	0.407
ICU length of stay in days (mean ± SD)	2.8 ± 8.1	1.5 ± 4.1	2.3 ± 6.6	0.7	0.500
Intubation required, n (%)	6 (17.6)	7 (9.7)	36 (11.7)	1.4	0.496
Days on intubation (mean ± SD)	2.7 ± 8.3	0.6 ± 2.1	1.3 ± 5.7	1.8	0.168

df = 2; $p < 0.05$ is statistically significant

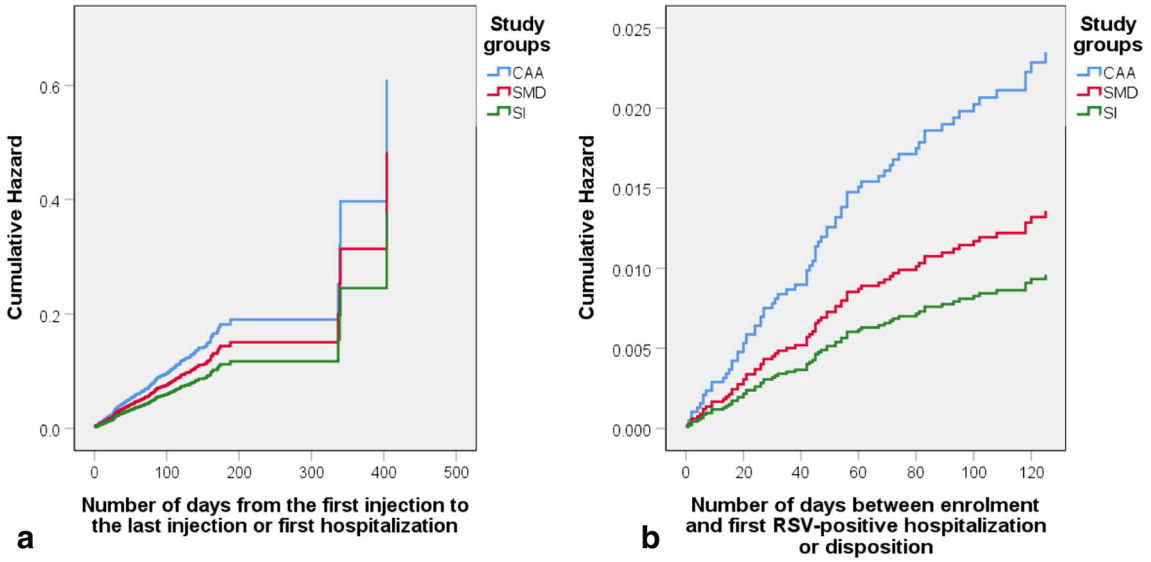

Fig. 1 Time to first respiratory illness hospitalization (Cox proportional hazard analysis, **a**) and first RSV-related hospitalization (Cox proportional hazard analysis, **b**). RIH: CAA versus SI (HR = 1.6, 95% CI 1.2–2.2, $p = 0.002$; RSVH: CAA versus SI (HR = 2.1, 95% CI 1.0–4.4, $p = 0.037$)

Despite the restrictive recommendations from pediatric advisory bodies [16–18] for RSV prophylaxis in children with a CAA, the question remains as to whether palivizumab should be offered to this high-risk population. Gaboli et al. [34] attempted to establish a consensus among Spanish pulmonologists with regard to the appropriateness of the off-label use of palivizumab in children with a wide spectrum of respiratory diseases. In this Delphi study, concordance was reached in 55.8% (24/43) of the statements. Agreement regarding CAA was that prophylaxis should be provided to children with tracheo-esophageal fistula and tracheo-malacia until 12 months of age at the onset of the RSV epidemic season. For children with bronchopulmonary malformations and respiratory symptoms, RSV prophylaxis was recommended until 2 years of age. The Canadian RSV Evaluation Study of Palivizumab investigators first reported on a series of 952 children who had pre-existing medical disorders and received palivizumab between the 2006–2010 RSV seasons. One hundred seventy-eight (18.7%) had airway anomalies, 18 of which were hospitalized for a respiratory-related illness. The RIH rate was 10.1% while the RSVH rate was documented as 2.7% [35]. In the combined Torino-Verona-Canadian prospective study, conducted over 13 RSV seasons from 2001 to 2014, of children who had received palivizumab, 353 (7.3%) had a CAA [12]. The cumulative incidence of RSVH in children with a CAA was 6.0% (95% CI 3.5–8.4). In the multivariate regression analysis controlling for risk factors associated with RSVH, children with a CAA compared with preterm infants had an odds ratio of 2.7 (95%CI 1.7–4.3; $p < 0.001$) of being hospitalized with RSV. The authors concluded that

Table 5 Risk of hospitalization due to respiratory illness or respiratory syncytial virus in subjects with a CAA ($n = 1219$) compared to SI ($n = 20,246$) and CMD ($n = 3538$)

	Adjusted HR*	95% CI	*p* value
RIH			
CAA versus SI	1.6	1.2–2.2	*0.002*
CAA versus SMD	1.3	0.9–1.9	0.190
RSVH			
CAA versus SI	2.1	1.0–4.4	*0.037*
CAA versus SMD	1.7	0.7–4.1	0.277

*Cox regression analysis adjusting for gender, ethnicity, proportion of aboriginals, daycare attendance, smoking exposure in home, number of siblings, number of sibling in daycare or school aged, multiple birth status, equal to greater than 5 people in the household, atopy, enrollment age and weight, gestational age and birth weight, days of neonatal stay, respiratory support and duration, oxygen therapy and duration, documented necrotizing enterocolitis, surgery for patent ductus arteriosus, documented sepsis, and number of palivizumab injections

df = 2; $p < 0.05$ is statistically significant

Table 6 Post-hoc analysis. Risk of hospitalization due to respiratory illness or respiratory syncytial virus in subjects with upper congenital airway anomalies ($n = 666$) compared to those with lower congenital airway anomalies ($n = 553$)

RIH			
	Adjusted HR*	95% CI	*p* value
Upper CAA	0.9	0.5–1.4	0.599
Lower CAA	1		
RSVH			
	Adjusted HR*	95% CI	*p* value
Upper CAA	1.8	0.5–6.2	0.365
Lower CAA	1		

*Cox regression analysis adjusted for gender, proportion of aboriginals, daycare attendance, exposure to smoking, days of neonatal stay, respiratory support and duration, oxygen therapy duration, sepsis, surgery for patent ductus arteriosus, and enrollment weight

df = 2; $p < 0.05$ is statistically significant

Table 7 Post hoc analysis. Risk of hospitalization due to respiratory illness or respiratory syncytial virus in subjects primarily prophylaxed for congenital airway anomalies ($n = 852$) compared to those with standard indications ($n = 20,246$) and complex medical disorders ($n = 3538$)

RIH			
	Adjusted HR**	95% CI	*p* value
CAA only versus SI	1.7	1.2–2.4	*0.003*
CAA only versus SMD	1.5	1.0–2.2	*0.042*
RSVH			
	Adjusted HR**	95% CI	*p* value
CAA only versus SI	2.1	0.8–5.6	0.123
CAA only versus SMD	1.4	0.5–4.1	0.512

**Cox regression analysis adjusting for gender, ethnicity, proportion of aboriginals, daycare attendance, smoking exposure in home, number of siblings, number of sibling in daycare or school aged, multiple birth status, equal to greater than 5 people in the household, atopy, enrollment age and weight, gestational age, days of neonatal stay, respiratory support and duration, oxygen therapy, documented necrotizing enterocolitis, surgery of patent ductus arteriosus, documented sepsis, and number of injections

df = 2; $p < 0.05$ is statistically significant

increased attention should be devoted to children with serious medical disorders such as CAA, who are independently at high risk for severe RSV disease despite prophylaxis.

Our study of children with a CAA comprises the largest group internationally who have received RSV prophylaxis and have been prospectively followed for RIH and RSVH. The findings confirm yet again that this cohort of children are not surprisingly at increased risk for overall RIH compared to the group with other SMDs and those prophylaxed for SIs. The RSVH rate was 2.4% compared to the Manzoni et al. [12] study and in part may be explained by the high and perfect adherence rates as defined in our results that were achieved longitudinally through the RSV seasons. The RSVH rate in the current study is also similar to our previous reported rate of 2.7% [35] which demonstrates consistency and efficacy of the approved protocol of 5 monthly injections of palivizumab during each RSV season. Alternatively, as previously reported [12], the increased risk of RSVH may reflect a baseline, higher risk for RSVH among infants with a CAA or that prophylaxis in this cohort may be less effective. It is important to note that the protocol for 5 monthly injections of palivizumab during the RSV season aligns with the pharmacokinetics and authorization of palivizumab irrespective of pre-existing complex medical disorders. Perhaps, revised dosing schedules merit exploration, to further reduce the incidence of RSVH in children with a CAA.

Our study affords national generalizability and applicability of the assembled data but several limitations of the study deserve consideration. First, the magnitude of the effect of palivizumab in children with a CAA cannot be estimated in the absence of a control group. However, extrapolating from the Danish RSV study [11], the mean RSVH rate for unprophylaxed children with a CAA was 9.4%. Using our data of a RSVH incidence of 2.4% in children with a CAA who received prophylaxis, palivizumab may achieve a 74.5% reduction in RSVH in this population with a number needed to treat of 13 to avoid one hospitalization. Second, the types of CAA lesions varied and the anatomical site may pose different risks for RIH and RSVH hospitalization but this was not evident in our study. Third, all patients may not be captured since enrollment in our registry is by voluntary consent. Fourth, the incidence of RSV is likely underestimated, since all patients were not routinely tested for RSV following admission to hospital. Last, the CAA sample size albeit the largest overall, was smaller compared to the SMD and SI groups. This may have compromised our ability to show a RSVH difference between the groups. On the contrary, the results may indicate that palivizumab is just as effective in reducing RSVH in this cohort of children as in children with other SMDs and those who received palivizumab for standard, approved indications.

Conclusions

Children with both upper and lower airway anomalies are a high-risk group for RIH because of their anatomical aberrations. They are equally at significant risk for RSVH with accompanying potential morbidity. This prospective study confirms that even with prophylaxis, the risk of RSVH although low, persists through the first 2 years of life. Our findings establish that children with a CAA require careful surveillance during the RSV season and should be considered for prophylaxis. Multicenter prospective studies are necessary to confirm the efficacy of palivizumab in this population.

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Authors' contributions Dr. Paes conceptualized the study, drafted the first version of the manuscript, and reviewed and edited the final version of the manuscript. Doyoung Kim, Mahwesh Saleem, and Sophie Wong were instrumental in the data assembly and analyses and the development of the tables and figures for submission. Dr. Ian Mitchell and Dr. Krista Lanctot critically reviewed the analyses and interpretation of the data and edited the final version for submission. All authors confirm responsibility for the reported research and have approved the manuscript as submitted.

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Compliance with ethical standards

Conflict of interest The Canadian RSV Evaluation Study of Palivizumab is funded by an investigator-initiated grant from AbbVie Canada. However, AbbVie had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. Bosco Paes, Ian Mitchell, and Krista Lanctôt have received research funding from AbbVie Corporation and compensation as advisors or lecturers from AbbVie Corporation and MedImmune. Doyoung Kim, Mahwesh Saleem, and Sophie Wong declare they have no conflict of interest.

Ethical approval Investigators in all 32 Canadian sites where the Canadian RSV Evaluation Study of Palivizumab study was conducted received ethical approval from their respective institutional research boards.

Informed consent All subjects were enrolled following full prior consent by parents or the legal guardian of the child.

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